ALDURAZYME® (LARONIDASE)

Solution for Intravenous Infusion Only

WARNING

Risk of anaphylaxis.

Life-threatening anaphylactic reactions have been observed in some patients during ALDURAZYME infusions. Therefore, appropriate medical support should be readily available when ALDURAZYME is administered. Patients with compromised respiratory function or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory compromise due to infusion reactions, and require additional monitoring.

DESCRIPTION

ALDURAZYME® (laronidase) is a polymorphic variant of the human enzyme, α-L-iduronidase that is produced by recombinant DNA technology in a Chinese hamster ovary cell line. α-L-iduronidase (glycosaminoglycan α-L-iduronohydrolase, EC 3.2.1.76) is a lysosomal hydrolase that catalyses the hydrolysis of terminal α-L-iduronic acid residues of dermatan sulfate and heparan sulfate.

Laronidase is a glycoprotein with a molecular weight of approximately 83 kD. The predicted amino acid sequence of the recombinant form, as well as the nucleotide sequence that encodes it, are identical to a polymorphic form of human α-L-iduronidase. The recombinant protein is comprised of 628 amino acids after cleavage of the N-terminus and contains 6 N-linked oligosaccharide modification sites. Two oligosaccharide chains terminate in mannose-6-phosphate sugars. ALDURAZYME has a specific activity of approximately 172 U/mg.

ALDURAZYME, for intravenous infusion, is supplied as a sterile, nonpyrogenic, colorless to pale yellow, clear to slightly opalescent solution that must be diluted prior to administration in 0.9% Sodium Chloride Injection, USP, containing 0.1% Albumin (Human). The solution in each vial contains a nominal laronidase concentration of 0.58 mg/mL and a pH of approximately 5.5. The extractable volume of 5.0 mL from each vial provides 2.9 mg laronidase, 43.9 mg sodium chloride, 63.5 mg sodium phosphate monobasic monohydrate, 10.7 mg sodium phosphate dibasic heptahydrate, and 0.05 mg polysorbate 80. ALDURAZYME does not contain preservatives; vials are for single use only.

CLINICAL PHARMACOLOGY

Mechanism of Action

Mucopolysaccharide storage disorders are caused by the deficiency of specific lysosomal enzymes required for the catabolism of glycosaminoglycans (GAG). Mucopolysaccharidosis I (MPS I) is characterized by the deficiency of α-L-iduronidase, a lysosomal hydrolase which catalyses the hydrolysis of terminal α-L-iduronic acid residues of dermatan sulfate and heparan sulfate. Reduced or absent α-L-iduronidase activity results in the accumulation of the GAG substrates, dermatan sulfate and heparan sulfate, throughout the body and leads to widespread cellular, tissue, and organ dysfunction.

The rationale of ALDURAZYME therapy in MPS I is to provide exogenous enzyme for uptake into lysosomes and increase the catabolism of GAG. ALDURAZYME uptake by cells into lysosomes is most likely mediated by the mannose-6-phosphate-terminated oligosaccharide chains of laronidase binding to specific mannose-6-phosphate receptors.

Because many proteins in the blood are restricted from entry into the central nervous system by the blood brain barrier, effects of intravenously administered ALDURAZYME on cells within the central nervous system (CNS) cannot be inferred from activity in sites outside the CNS. The ability of ALDURAZYME to cross the blood brain barrier has not been evaluated in animal models or in clinical trials.

Pharmacokinetics

The pharmacokinetics of laronidase were evaluated in 12 patients with MPS I who received 0.58 mg/kg of ALDURAZYME as a 4-hour infusion. After the 1st, 12th and 26th weekly infusions, the mean maximum plasma concentrations (C_{max}) ranged from 1.2 to 1.7 mcg/mL for the 3 time points. The mean area under the plasma concentration-time curve (AUC_∞) ranged from 4.5 to 6.9 mcg • hour/mL. The mean volume of distribution (V_d) ranged from 0.24 to 0.6 L/kg. Mean plasma clearance (CL) ranged from 1.7 to 2.7 mL/min/kg, and the mean elimination half-life ($t_{1/2}$) ranged from 1.5 to 3.6 hours.

Effects of Antibodies

Most patients who received once-weekly infusions of ALDURAZYME developed antibodies to laronidase by week 12. Between weeks 1 and 12, increases in plasma clearance of laronidase were observed in some patients which appeared to be proportional to the antibody titer. At week 26, plasma clearance of laronidase was comparable to that at week 1, in spite of the continued and, in some cases, increased titers of antibodies.

CLINICAL STUDIES

ALDURAZYME was studied in a randomized, placebo-controlled clinical trial of 45 MPS I patients of whom 1 patient was clinically assessed as having the Hurler form, 37 Hurler-Scheie, and 7 Scheie. All patients had a baseline forced vital capacity (FVC) less than or equal to 77% of predicted. Patients received ALDURAZYME at 0.58 mg/kg or placebo once-weekly for 26 weeks. All patients were treated with antipyretics and antihistamines prior to each infusion.

The primary efficacy outcome assessments were FVC and distance walked in 6 minutes (6 minute walk test, 6MWT). After 26 weeks, patients treated with ALDURAZYME showed improvement in FVC and in 6MWT compared to placebo-treated patients (**see Table 1**).

Table 1: Primary Efficacy Outcomes

		ALDURAZYME N = 22	Placebo N = 23
Forced Vital Capacity (percent of predicted normal)			
Baseline	Mean ± s.d.	48 ± 15	54 ± 16
Week 26	Mean ± s.d.	50 ± 17	51 ± 13
Change from baseline to week 26	Mean ± s.d.	1 ± 7	-3 ± 7
	Median	1	-1
Difference between groups	Mean	4	
	Median (95% CI)	2 (0.4, 7) p=0.02*	
6-Minute Walk Distance (meters)			
Baseline	Mean ± s.d.	319 ± 131	367 ± 114
Week 26	Mean ± s.d.	339 ± 127	348 ± 129
Change from baseline to week 26	Mean ± s.d.	20 ± 69	-18 ± 67
	Median	28	-11
Difference between groups	Mean	38	
	Median (95% CI)	39 (-2, 79) p=0.07*	

*By Wilcoxon Rank Sum Test

Evaluations of bioactivity were changes in liver size and urinary GAG levels. Liver size and urinary GAG levels decreased in patients treated with ALDURAZYME compared to patients treated with placebo. No subject in the group receiving ALDURAZYME reached the normal range for urinary GAG levels during this 6-month study.

All 45 patients received open-label ALDURAZYME for 36 weeks following the double-blind period. Maintenance of mean FVC and an additional increase in mean 6MWT distance were observed compared to the start of the open-label period among patients who were initially randomized to and then continued to receive ALDURAZYME.

Among patients who had been initially randomized to placebo, improvements from baseline in mean FVC and 6MWT distance were observed compared to the start of the open-label period.

INDICATIONS AND USAGE

ALDURAZYME is indicated for patients with Hurler and Hurler-Scheie forms of Mucopolysaccharidosis I (MPS I) and for patients with the Scheie form who have moderate to severe symptoms. The risks and benefits of treating mildly affected patients with the Scheie form have not been established.

ALDURAZYME has been shown to improve pulmonary function and walking capacity. ALDURAZYME has not been evaluated for effects on the central nervous system manifestations of the disorder.

CONTRAINDICATIONS

There are no known contraindications to the use of ALDURAZYME.

WARNINGS

Anaphylaxis and Allergic Reactions (see BOXED WARNING)

Life-threatening anaphylactic reactions have been observed in some patients during or up to 3 hours after ALDURAZYME infusions. Reactions have included: respiratory failure, respiratory distress, stridor, tachypnea, bronchospasm, airway obstruction, hypoxia, hypotension, bradycardia, and urticaria. Interventions have included: resuscitation, mechanical ventilatory support, emergency tracheotomy, hospitalization, and treatment with inhaled beta-adrenergic agonists, epinephrine, and intravenous corticosteroids.

In clinical trials and postmarketing safety experience with ALDURAZYME, approximately 1% of patients experienced severe or serious allergic reactions. In patients with MPS I, pre-existing upper airway obstruction may have contributed to the severity of some reactions. Due to the potential for severe allergic reactions, appropriate medical support should be readily available when ALDURAZYME is administered. Because of the potential for recurrent reactions, some patients who experience initial severe reactions may require prolonged observation.

Patients with an acute illness at the time of ALDURAZYME infusion may be at greater risk for infusion-related reactions. Careful consideration should be given to the patient's clinical status prior to administration of ALDURAZYME. One patient with acute bronchitis and hypoxia experienced increased tachypnea during the first ALDURAZYME infusion that resolved without intervention. The patient's respiratory symptoms returned within 30 minutes of completing the infusion and responded to bronchodilator therapy. Approximately 6 hours after the infusion, the patient experienced coughing, then respiratory arrest, and died.

Patients should receive antipyretics and/or antihistamines prior to infusion (see **ADVERSE REACTIONS**). If an infusion reaction occurs, regardless of pretreatment, decreasing the infusion rate, temporarily stopping the infusion, and/or administration of additional antipyretics and/or antihistamines may ameliorate the symptoms (see **ADVERSE REACTIONS**).

If anaphylactic or other severe allergic reactions occur, immediately discontinue the infusion of ALDURAZYME and initiate appropriate treatment. Caution should be exercised if epinephrine is being considered for use in patients with MPS I due to the increased prevalence of coronary artery disease in these patients.

The risks and benefits of re-administering ALDURAZYME following an anaphylactic or severe allergic reaction should be considered. Extreme care should be exercised, with appropriate resuscitation measures available, if the decision is made to re-administer the product.

PRECAUTIONS

Information for Patients

Patients should be informed that a registry for MPS I patients has been established in order to better understand the variability and progression of MPS I disease, and to continue to monitor and evaluate treatments. Patients should be encouraged to participate and advised that their participation may involve long-term follow-up.

Information regarding the registry program may be found at www.MPSIregistry.com or by calling (800) 745-4447.

Drug Interactions

No formal drug interaction studies have been conducted.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies to assess the mutagenic and carcinogenic potential of ALDURAZYME have not been conducted.

Reproductive studies in rats have not demonstrated impairment of fertility (see **PRECAUTIONS: Pregnancy**).

Pregnancy: Category B

Reproduction studies have been performed in male and female rats at doses up to 6.2 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ALDURAZYME. However, there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ALDURAZYME should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ALDURAZYME is administered to a nursing woman (see **PRECAUTIONS: Information for Patients** regarding a registry program. Nursing women are encouraged to participate in this program.).

Pediatric Use

Patients younger than 5 years of age were not included in the clinical studies because of inability to comply with efficacy outcome assessments. It is not known if children younger than 5 years of age respond differently from older children.

Geriatric Use

Clinical studies of ALDURAZYME did not include patients aged 65 and over. It is not known whether they respond differently from younger patients.

ADVERSE REACTIONS

The most serious adverse reactions reported with ALDURAZYME during clinical trials and the postmarketing period were anaphylactic and allergic reactions (see **BOXED WARNING** and **WARNINGS: Anaphylaxis and Allergic Reactions**).

The most common adverse reactions associated with ALDURAZYME treatment in the clinical studies were upper respiratory tract infection, rash, and injection site reaction.

In clinical studies, the most common adverse reactions requiring intervention were infusion-related reactions reported in 32% (7 of 22) of patients treated with ALDURAZYME. The most common infusion-related reactions were flushing, fever, headache, and rash. Flushing occurred in 5 patients (23%) receiving ALDURAZYME; the other reactions were less frequent. Infusion-related reactions were not significantly different between the ALDURAZYME treatment group and the placebo treatment group who received infusions of diluent and all components of ALDURAZYME except the laronidase enzyme. All reactions were classified as being mild to moderate in severity. The frequency of infusion-related reactions decreased with continued use during the open-label extended use period. Less common infusion-related reactions include: cough, bronchospasm, dyspnea, urticaria, angioedema, and pruritus. Most infusion-related reactions requiring intervention were ameliorated with slowing of the infusion rate, temporarily stopping the infusion, and/or administering additional antipyretics and/or antihistamines.

The data described below reflect exposure to 0.58 mg/kg of ALDURAZYME for 26 weeks in a placebo-controlled double-blind study in 45 patients with MPS I (N=22 ALDURAZYME, and N=23 placebo). All 45 patients continued into an open-label study of ALDURAZYME treatment for an additional 36 weeks. An additional 10 patients participated in a Phase 1 open-label study with continued infusions for up to 3 years. The population in the placebo-controlled study was evenly distributed for gender (N=23 females and 22 males) and ranged in ages from 6 to 43 years. Of the 45 patients in the placebo-controlled study, 1 was clinically assessed as having Hurler form, 37 Hurler-Scheie, and 7 Scheie. All patients were treated with antipyretics and antihistamines prior to the infusions.

Because clinical trials are conducted under widely varying and controlled conditions, the observed adverse reaction rates may not predict the rates observed in patients in clinical practice.

Table 2 enumerates adverse events and selected laboratory abnormalities that occurred during the placebo-controlled trial in at least 2 patients more in the ALDURAZYME group than was observed in the placebo group. Reported adverse events have been classified using standard WHOART terms. Observed adverse events in the Phase 1 study and the open-label treatment period following the controlled study were not different in nature or severity.

Table 2: Number and (%) of Patients with Adverse Events and Selected Laboratory Abnormalities in the Placebo-Controlled Study

Adverse Event	Placebo (N = 23)	ALDURAZYME (N = 22)
Respiratory System		
Upper respiratory tract infection	4 (17)	7 (32)
Body as a Whole		
Chest pain	0	2 (9)
Nervous System		
Hyperreflexia	0	3 (14)
Paresthesia	1 (4)	3 (14)
Skin and Appendages		
Rash	5 (22)	8 (36)
Resistance Mechanism		
Abscess	0	2 (9)
Liver and Biliary System		
Bilirubinemia	0	2 (9)
Vascular		
Vein disorder	1 (4)	3 (14)
Urinary System		
Facial edema	0	2 (9)
Cardiovascular, General		
Hypotension	0	2 (9)
Dependent edema	0	2 (9)
Vision		
Corneal opacity	0	2 (9)
Application Site		
Injection site pain	0	2 (9)
Injection site reaction	2 (9)	4 (18)
Platelet, Bleeding and Clotting		
Thrombocytopenia	0	2 (9)

In postmarketing experience with ALDURAZYME, severe and serious infusion-related reactions have been reported, some of which were life-threatening (see **BOXED WARNING** and **WARNINGS: Anaphylaxis and Allergic Reactions**). The most frequently reported adverse reactions (using MedDRA terminology) included: chills, vomiting, nausea, arthralgia, diarrhea, tachycardia, abdominal pain, blood pressure increased, and oxygen saturation decreased.

Immunogenicity

In clinical studies, 50 of 55 patients (91%) treated with ALDURAZYME were positive for antibodies to laronidase. The clinical significance of antibodies to ALDURAZYME is not known, including the potential for product neutralization.

The data reflect the percentage of patients whose test results were considered positive for antibodies to ALDURAZYME using an enzyme-linked immunosorbent assay (ELISA) for laronidase-specific IgG binding antibodies, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibodies in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ALDURAZYME with the incidence of antibodies to other products may be misleading.

Four patients in the controlled study who experienced severe infusion-related reactions were tested for ALDURAZYME-specific IgE antibodies and complement activation. IgE testing was performed by ELISA and complement activation was measured by the Quidel Enzyme Immunoassay. One of the four patients had an anaphylactic reaction consisting of urticaria and airway obstruction and tested positive for both ALDURAZYME-specific IgE binding antibodies and complement activation (see **BOXED WARNING** and **WARNINGS: Anaphylaxis and Allergic Reactions**).

Other allergic reactions were also seen in patients receiving ALDURAZYME (see **ADVERSE REACTIONS**).

OVERDOSAGE

There is no experience with overdoses of ALDURAZYME.

DOSAGE AND ADMINISTRATION

The recommended dosage regimen of ALDURAZYME is 0.58 mg/kg of body weight administered once-weekly as an intravenous infusion.

Pretreatment with antipyretics and/or antihistamines is recommended 60 minutes prior to the start of the infusion (see **WARNINGS: Anaphylaxis and Allergic Reactions**).

The total volume of the infusion is determined by the patient's body weight and should be delivered over approximately 3 to 4 hours. Patients with a body weight of 20 kg or less should receive a total volume of 100 mL. Patients with a body weight of greater than 20 kg should receive a total volume of 250 mL. The initial infusion rate of 10 mcg/kg/hr may be incrementally increased every 15 minutes during the first hour, as tolerated, until a maximum infusion rate of 200 mcg/kg/hr is reached. The maximum rate is then maintained for the remainder of the infusion (2-3 hours).

For Patients Weighing 20 kg or Less	
Total Volume of ALDURAZYME Infusion = 100 mL	
2 mL/hr x 15 minutes (10 mcg/kg/hr)	Obtain vital signs, if stable then increase the rate to...
4 mL/hr x 15 minutes (20 mcg/kg/hr)	Obtain vital signs, if stable then increase the rate to...
8 mL/hr x 15 minutes (50 mcg/kg/hr)	Obtain vital signs, if stable then increase the rate to...
16 mL/hr x 15 minutes (100 mcg/kg/hr)	Obtain vital signs, if stable then increase the rate to...
32 mL/hr x ~3 hours (200 mcg/kg/hr)	For the remainder of the infusion.

For Patients Weighing Greater than 20 kg	
Total Volume of ALDURAZYME Infusion = 250 mL	
5 mL/hr x 15 minutes (10 mcg/kg/hr)	Obtain vital signs, if stable then increase the rate to...
10 mL/hr x 15 minutes (20 mcg/kg/hr)	Obtain vital signs, if stable then increase the rate to...
20 mL/hr x 15 minutes (50 mcg/kg/hr)	Obtain vital signs, if stable then increase the rate to...
40 mL/hr x 15 minutes (100 mcg/kg/hr)	Obtain vital signs, if stable then increase the rate to...
80 mL/hr x ~3 hours (200 mcg/kg/hr)	For the remainder of the infusion.

Each vial of ALDURAZYME provides 2.9 mg of laronidase in 5.0 mL of solution and is intended for single use only. Do not use the vial more than one time. The concentrated solution for infusion must be diluted with 0.1% Albumin (Human) in 0.9% Sodium Chloride Injection, USP using aseptic techniques. ALDURAZYME should be prepared using PVC containers and administered with a PVC infusion set equipped with an in-line, low protein binding 0.2 micrometer (µm) filter. There is no information on the compatibility of diluted ALDURAZYME with glass containers.

Instructions for Use (Aseptic Techniques)

1. Determine the number of vials to be diluted based on the individual patient's weight and the recommended dose of 0.58 mg/kg [Patient's weight (kg) x 1 mL/kg of ALDURAZYME = Total # mL of ALDURAZYME, then Total # of mL of ALDURAZYME ÷ 5 mL per Vial = Total # of Vials]. Round up to the nearest whole vial. Remove the required number of vials from the refrigerator to allow them to reach room temperature. Do not heat or microwave vials.
2. Before withdrawing the ALDURAZYME from the vial, visually inspect each vial for particulate matter and discoloration. The ALDURAZYME solution should be clear to slightly opalescent and colorless to pale yellow. A few translucent particles may be present. Do not use if the solution is discolored or if there is particulate matter in the solution.
3. Determine the total volume of the infusion to be used based on the patient's body weight. The total final volume should be either 100 mL (if weight is less than or equal to 20 kg) or 250 mL (if weight is greater than 20 kg).
4. Using the chart below, prepare an infusion bag of 0.1% Albumin (Human) in 0.9% Sodium Chloride Injection, USP. Remove and discard a volume of 0.9% Sodium Chloride Injection, USP equal to the volume of Albumin (Human) to be added to the infusion bag. Add the appropriate volume of Albumin (Human) to the infusion bag and gently rotate the infusion bag to ensure proper distribution of the Albumin.

Total Volume of ALDURAZYME Infusion	Volume of Albumin (Human) 5% to be Added	Volume of Albumin (Human) 25% to be Added
100 mL	2 mL	0.4 mL
250 mL	5 mL	1 mL

5. Withdraw and discard a volume of the 0.1% Albumin (Human) in 0.9% Sodium Chloride Injection, USP from the infusion bag, equal to the volume of ALDURAZYME concentrate to be added.
6. Slowly withdraw the calculated volume of ALDURAZYME from the appropriate number of vials using caution to avoid excessive agitation. Do not use a filter needle, as this may cause agitation. Agitation may denature ALDURAZYME, rendering it biologically inactive.
7. Slowly add the ALDURAZYME solution to the 0.1% Albumin (Human) in 0.9% Sodium Chloride Injection, USP using care to avoid agitation of the solutions. Do not use a filter needle.
8. Gently rotate the infusion bag to ensure proper distribution of ALDURAZYME. Do not shake the solution.

ALDURAZYME does not contain any preservatives; therefore, after dilution with saline in the infusion bags, any unused product or waste material should be discarded and disposed of in accordance with local requirements.

ALDURAZYME must not be mixed with other medicinal products in the same infusion.

The compatibility of ALDURAZYME in solution with other products has not been evaluated.

STORAGE

Store ALDURAZYME under refrigeration at 2°C to 8°C (36°F to 46°F). DO NOT FREEZE OR SHAKE. DO NOT USE ALDURAZYME after the expiration date on the vial. This product contains no preservatives.

The diluted solution should be used immediately. If immediate use is not possible, the diluted solution should be stored refrigerated at 2°C to 8°C (36°F to 46°F). The in-use storage should not be longer than 36 hours from the time of preparation to completion of administration. Room temperature storage of diluted solution is not recommended.

HOW SUPPLIED

ALDURAZYME is supplied as a sterile solution in clear Type I glass 5 mL vials (2.9 mg laronidase per 5 mL). The closure consists of a siliconized butyl stopper and an aluminum seal with a plastic flip-off cap.

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Rx Only

ALDURAZYME is manufactured by:
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